**Title**: Ferric carboxymaltose (Ferinject®) associated hypophosphataemia: case report illustrating the need for increased awareness to minimise incidence and risk.

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**Author contributions:**

SF is the case patient, conceived the research idea, critically revised and approved final version of the paper. LJ performed the research and analysed the data, and wrote the paper.

**Key learning points**

- Ferric carboxymaltose (Ferinject®) associated hypophosphataemia is a potentially underreported adverse effect in patients treated for iron-deficiency anaemia.
- Previous literature involving some cases has suggested it is reversible through phosphate supplementation, but this further upregulated renal phosphate excretion.
- Standard acute medicine protocols for treating hypophosphataemia do not apply in such instances, and a conservative approach should be adopted.
- Ferric carboxymaltose (Ferinject®) associated hypophosphataemia appears to usually resolve some seven weeks after the iron infusion.

**MCQs**

1. Ferric carboxymaltose (Ferinject®) associated hypophosphataemia should primarily be managed:

a. with multiple high dose phosphate infusions

b. conservatively (watch and wait)

c. oral phosphate (effervescent tablets)

d. in accordance with standard hospital protocol for hypophosphataemia

2. Apart from serum phosphate measurement, which other two biochemical measurements should definitely be measured to avoid further acute complications?

a. vitamin D and magnesium levels

b. vitamin D and calcium levels

c. calcium and iron levels

d. calcium and potassium levels

**Abstract**

Ferric carboxymaltose (Ferinject®) is an infusion administered for the treatment of iron deficiency anaemia. A number of previous case reports have shown the occurrence of hypophosphataemia after Ferinject® treatment, supposedly managed though high dose phosphate therapy. This case report highlights the risk associated with, and futility of, managing this adverse effect through high dose phosphate infusion. A review of the available literature suggests that if hypophosphataemia develops as a result of Ferinject®, through upregulation of the renal protein Fibroblast Growth Factor-23, it cannot be readily reversed and on average persists for circa 50 days. Acute medical units should be aware of this – likely underreported – adverse effect, and avoid treating these hypophosphataemic patients with high dose phosphate since it can compound symptoms.

**Keywords**

Ferinject®; ferric carboxymaltose; hypophosphataemia; iron-deficiency anaemia; phosphate

**Case report**

In specific scenarios where iron deficiency anaemia patients are intolerant or not responding to oral supplementation, parenteral supplementation through intravenous infusion of iron is recommended.[1,2] Ferric carboxymaltose (Ferinject®) is commonly used due to the relatively short infusion time. We present a case of Ferinject®-associated severe hypophosphataemia and share the journey experienced by the patient in question. Furthermore, we utilise a review of the existing literature to make the case for increased awareness and guidelines on this side effect. **High dose phosphate replacement is not indicated in patients who are admitted to an acute unit with hypophosphataemia related to iron infusion.**

A 40-year-old female attended a nurse-led haematology out-patient clinic to receive 1000 mg Ferinject® iv on 12 November 2019. She had received an identical treatment 12 months prior, due to ongoing low haemoglobin levels related to poor absorption of oral iron supplementation related to coeliac disease. After the first infusion, she had only noticed an improvement in fatigue symptoms after approximately two months. Subsequent to the second Ferinject® infusion, day 0, symptoms typical of iron deficiency anaemia had again not abated and fatigue, shortness of breath on exertion and dizziness continued. Upon a visit to the GP at day 6, blood tests revealed hypophosphataemia (see Figure 1). A 500 mmol phosphate infusion was administered in line with local Trust protocol for hypophosphataemia. However, serum phosphate levels did not return to within normal range, and the above symptoms worsened to a stage where the patient presented to the Emergency Department on day 8. There, another 500 mmol phosphate infusion was commenced – which had to be reduced to 200 mmol at a much lower infusion rate (from 50 mmol/hr to 20 mmol/hr) due to an episode of severe hypocalcaemia, resolved by injection of calcium 2.25 mmol iv. Based on consultation of selected literature[3,4], a further four 200-500 mmol phosphate infusions were administered and vitamin D supplementation was initiated. At this stage, the hospital protocol for phosphate infusion was breached. Due to anxiety induced by this episode – particularly the extremely low serum phosphate levels - and a putative respective induction effect on serum phosphate levels and inhibitory effect

on Fibroblast Growth Factor-23 (FGF23) levels, 40 mg/day propranolol was prescribed.[5,6] The main symptoms experienced by the patient were extreme fatigue, a profound sensation of pressure on the chest, and severe bone pain. At day 15, after further consultation of the literature and correspondence with Prof W Fraser (Director of Norfolk & Norwich University Hospital Bone Marker Service), phosphate infusions and propranolol were aborted. Serum phosphate levels and urinary phosphate excretion rates eventually returned to within normal range by day 42. Vitamin D supplementation and a high-phosphate diet were adhered to for a total of eight weeks. Over time, the chest and bone pain (the latter extended from sternum to back and all limbs, with added presence of a crushing headache) gradually reduced to a mild level by day 50. Overall, the episode resulted in a total of 8 weeks of sickness absence, with fatigue persisting beyond day 56.

Could this case of Ferinject®-associated severe hypophosphataemia have been prevented and is there a curative therapy for it? In terms of the latter, from the available published literature we would conclude that currently this type of hypophosphataemia cannot be instantly reversed and that it is a matter of patients 'sitting it out'. The mechanism that underlies the hypophosphataemia, upregulation of FGF23 in the kidneys, is known.[7] It appears that phosphate therapy further elevates FGF23 levels and thereby phosphate excretion; neither vitamin D (or its metabolites) nor propranolol affect FGF23 levels, and are therefore unlikely to contribute to correction of Ferinject®-related hypophosphataemia. Table 1 summarises published data on Ferinject® hypophosphataemia cases; an approximate median of 50 days appears to be the time period for phosphate levels to normalise again, regardless of attempts to actively reverse the hypophosphataemia or not. Prevention of Ferinject®-associated hypophosphataemia is therefore paramount. A potential benefit of measuring serum phosphate levels prior to Ferinject® infusion may be useful to avoid treating patients with existing hypophosphataemia. Nonetheless, as shown in Table 1, this side effect can also occur in patients with an in-range phosphate level. Phosphate measurement after Ferinject® infusion is indicated since the initial symptomology related to hypophosphataemia overlaps considerably with those associated with iron-deficiency anaemia, and it allows for a more exact quantification of the frequency of this debilitating side-effect. Further guidance by NHS Improvement, MHRA, or guidance by British Society for Haematology, akin to advice issued in New Zealand by Medsafe[8], may

help to increase awareness amongst haematologists and haematology specialist nurses. An addition to hospital phosphate infusion protocols highlighting that patients should be asked about recent iron infusions will inform wider medical specialties and avoid phosphate infusions where possible. Patients who consider Ferinject® therapy need to be consulted about the risk of hypophosphataemia and the average period this may persist. In our case, the patient was referred directly from primary care into a nurse-led iron infusion clinic. Currently, the Royal College of Nursing does not mention the potential for ferric carboxymaltose associated hypophosphataemia in its guideline on iron deficiency and anaemia.[9] Indeed, the patient in this case study was informed about the potential risk of anaphylaxis, but not of the risk of hypophosphataemia. The summary of product characteristics for Ferinject® does mention hypophosphataemia (but not that it currently cannot be readily reversed), and in most cases this is transient and without clinical symptoms, and that those cases requiring medical attention occurred mainly in patients with existing risk factors and after prolonged exposure to high-dose intravenous iron.[10] Uncertainty remains about the true extend of the risks involved due to variance in the literature.[11,12] Systematic recording and reporting of Ferinject® associated hypophosphataemia, though the MHRA's yellow card scheme is indicated to determine what the true risk and impact of ferric carboxymaltose associated hypophosphataemia is.

**Declaration of competing interests:** Nothing to declare.

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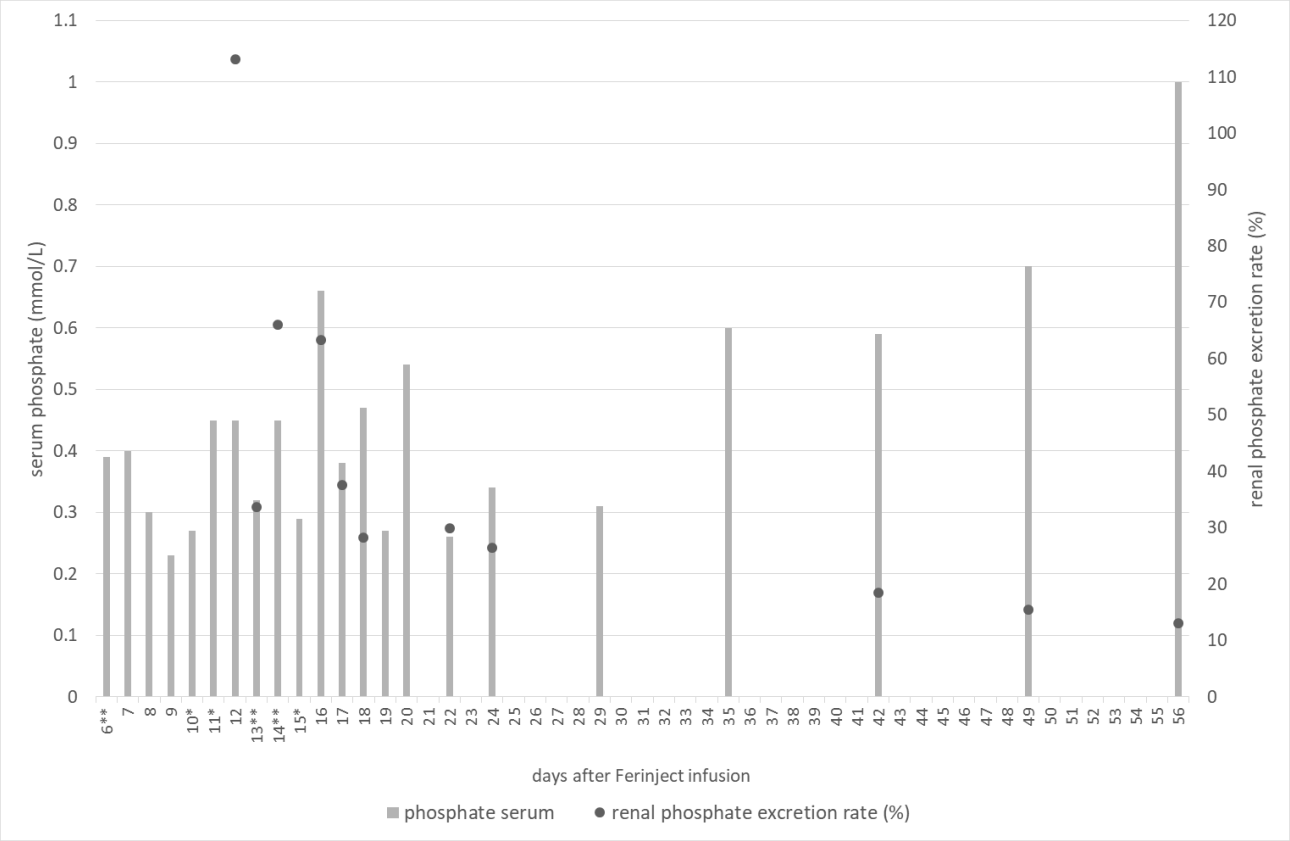
**MCQs – answers**

1. answer: b

2. answer: b

**Figure 1, Timeline of Ferinject® (ferric carboxymaltose) associated hypophosphataemia case, highlighting association between renal phosphate excretion rate (dot plot) and serum phosphate levels (bar chart)**




All phosphate measurements were taken around 9 AM, and prior to any phosphate infusions. **200 mmol phosphate infusion; * 500 mmol phosphate infusion.

**Table 1, Overview of publications regarding ferric carboxymaltose associated hypophosphataemia cases.**

| Reference | Ferric carboxymaltose dose [n patients] | Serum phosphate level (mmol/L) before infusion | Phosphate level (mmol/L) when presenting post-infusion | Days until hypophosphataemia resolved (level 0.8 mmol/L or higher) | Specific treatment/management post ferric carboxymaltose infusion |
|---|---|---|---|---|---|
| Wolf et al (2020)[12] | 750 mg on day 0 and 750 mg on day 7 [117] | Mean 1.07 | 65% of patients ≤0.64 at day 14 | 43% of patients ≤0.64 mmol/L at day 35 (final measuring point) | No information on management/treatment of hypophosphataemia |
| Ifie et al (2019)[3] | 500 mg [1] | 0.94 | 0.43 | 27 days | 15 doses of 15 mmol phosphate infusion across 4 weeks and daily oral phosphate, plus calcitriol 0.25ug daily, vitamin D3 800 U/day |
| Schaefer et al (2016)[13] | ≥ 500 mg [55] | <0.8 mmol/L in 15% of patients | 3.9% of patients <0.3, and 26% >0.3 to <0.5 (excluding existing the 15% of patients with pre-existing hypophosphataemia) | median of 84 days | No information on management/treatment of hypophosphataemia |
| Hardy & Vandemergel (2015)[14] | mean 2000 mg [78] | Mean 1.08 | 51% patients a level of <0.8, including 13% with level <0.32 | Mean hypophosphatemia duration of 6 months. Some patients received further ferric carboxymaltose infusions within follow-up period | No information on management/treatment of hypophosphataemia |
| Blazevic et al (2014)[4] | 1000 mg; 3x 1000 mg; 2x 1000 mg; 3x 1000 mg [4] | Not determined | 0.25; 0.32; 0.22; 0.28 | 36 days; 28 days; 60 days (level = 0.7); unknown | Iv phosphate, then oral; phosphate rich diet; iv phosphate and oral phosphate; |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | iv phosphate and oral phosphate, then calciferol |
| Mani et al (2010)[15] | 1500 - 3x 500 mg, 10 days apart [1] | 0.9 | 0.16 | 56 days (paper claims 2 weeks in text, but graph shows 8 weeks) | iv phosphate (dose not disclosed), then oral phosphate and calcitriol |
| Schouten et al (2009)[7] | 918 mg average [8] | Mean 1.2 | Mean 0.67 | At 42 days post-infusion, 6 out 8 cases within normal range. | No information on management/treatment of hypophosphataemia |